IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Enrico Anthony Antonini
Art Unit: 1625
Serial No.: 10/574,545
Filed: April 5, 2006
Confirmation No.: 4059
For: INDUSTRIAL METHOD FOR SEPARATION AND PURIFICATION OF FENTANYL BY REVERSE PHASE PREPARATIVE CHROMATOGRAPHY
Examiner: Nizal S. Charndrakumar

September 10, 2008

Declaration of Inventor Enrico Anthony Antonini

I, Enrico Anthony Antonini, declare as follows:

1. I am the sole inventor of the subject matter claimed in the above-entitled United States patent application, Serial Number 10/574,545.

2. I have reviewed the final Office action issued July 17, 2008 in this application, and the Hofstetter et al. (U.S. Patent No. 4,317,903) reference cited therein. I have reviewed all pending claims of this application, including claims 1 and 3-25.

3. The present invention is directed to an industrial process for recovering pure fentanyl, which as defined in the claims includes a phenethylpiperaniline impurity level of less than 0.010 weight percent, from an impure preparation comprising fentanyl containing phenethylpiperaniline. The process comprises subjecting the impure preparation to a reverse-phase high performance preparative liquid column chromatography, wherein a loading ratio of column media to fentanyl loaded onto the column is in the range of from about 50 to about 150. (See, e.g., pending claim 1.)

4. The Hofstetter reference discloses methods of using a reverse-phase high performance preparative liquid chromatography to obtain a highly pure preparation of the antibiotic lincomycin hydrochloride. The methods generally comprise a number of steps, including: (a) dissolving approximately 450 grams of the starting material (i.e., impure preparation of lincomycin A and lincomycin B) per liter of 30% aqueous methanol; (b) applying the solution to a chromatography column filled with 18 grams of C_{18} bonded phase silica gel per

gram of starting material; (c) stripping the remaining lincomycin from the column with 1 bed volume of methanol; (d) concentrating the lincomycin-rich eluate to dryness; (e) crystallizing the lincomycin according to standard crystallization procedure; (f) re-chromatographing the lincomycin B-rich fraction according to the above procedure; (g) concentrating the eluate containing greater than 98% lincomycin B to dryness; and (h) re-dissolving the solids in 3 milliliters of methanol per gram of lincomycin B solids at 40°C and adjusting the pH with concentrated hydrochloric acid to 1.5. (See, e.g., column 1, lines 48-68, and column 2, lines 1-6). Further, Hofstetter specifically discloses that a weight ratio of silica gel (i.e., the column media) to lincomycin in step (b) is "near optimum" at 18:1. (See, e.g., column 1, lines 54-58.)

5. Hofstetter does not disclose or suggest a process for producing pure fentanyl. Rather, Hofstetter discloses the recovery of lincomycin, which is a compound having a structure different from fentanyl.

6. Moreover, any use of analytical chromatography on narcotics, such as fentanyl, would guide one of ordinary skill in the art away from using preparative chromatography for an industrial scale process. Analytical chromatography typically involves loading a small mass of a feed onto a column, and using a small particle size material, typically less than 5 micrometers, in the stationary phase. This small particle size material generates much higher pressures than those found in typical preparative chromatography methods, mandating the use of large, strong and expensive chromatography equipment, which would negate the commercial viability for this process. Furthermore, in conventional preparative chromatography, the particle size of the stationary phase is small enough to achieve the separation, but is much larger than that used for analytical chromatography, the particle size typically being greater than 20 micrometers.

7. Prior to the present invention, precipitation and recrystallization were typically used for purifying fentanyl on an industrial scale. Accordingly, one of ordinary skill in the art would look to methods of improving the industrial precipitation and recrystallization processes for purifying fentanyl, not to chromatography methods, such as those used in the Hofstetter patent.

8. In view of the foregoing, the Hofstetter patent does not disclose or suggest a process for producing pure fentanyl as required in the instant claims.

9. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Enrico Anthony Antonini

09/24/08
Date